PATENT COOPERATION TREATY 09/744625

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

VOSSIUS & PARTNER
P.O. Box 86 07 67
D-81634 Munich
ALLEMAGNE

Date of mailing (day/month/year)
25 January 2001 (25.01.01)

Applicant's or agent's file reference
C 2130 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP99/05416

International filing date (day/month/year)
28 July 1999 (28.07.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
MICROMET GESELLSCHAFT FÜR
BIOMEDIZINISCHE FORSCHUNG MBH
Am Klopferspitz 19
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Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
MICROMET AG
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D-82152 Martinsried
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
S. De Michiel
Telephone No.: (41-22) 338.83.38

F ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 March 2000 (08.03.00)	
International application No. PCT/EP99/05416	**Applicant's or agent's file reference** C 2130 PCT
International filing date (day/month/year) 28 July 1999 (28.07.99)	**Priority date** (day/month/year) 28 July 1998 (28.07.98)
Applicant KUFER, Peter et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

28 January 2000 (28.01.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

F. Baechler

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C 2130 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/05416	28/07/1999	28/07/1998
International Patent Classification (IPC) or national classification and IPC		
C07K19/00		
Applicant		
MICROMET GESELLSCHAFT FÜR BIOMEDIZINISCHE FORSCHUN		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Auth rity (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/01/2000	27.10.00
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	SCHEFFZYK, I Télephone No. +49 89 2399 8602

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/05416

I. Basis of the r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-84	as originally filed				

Claims, No.:

1-41	as received on	20/07/2000	with letter of	19/07/2000	

Drawings, sheets:

1/75-75/75	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,4,8-18,20-25,27,30-32
	No:	Claims	1,2,5-7,19,26,28,29,33-41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-41
Industrial applicability (IA)	Yes:	Claims	1-41
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION V----------

Taking into account that according to claim 6 and also according to the specification of present application (see for instance page 1 and the examples) the domains having receptor or ligand function can be in the format of a scFv-fragment the subject-matter of claims 1,2, 5-7, 19, 26, 28, 29, 33-41 is considered to be anticipated by K. Müller et al., FEBS Letters, vol. 422, no. 2, 30.01.98, pp. 259-264 (1), see e.g. figure 1 and section Materials and Methods. It is correct that the heterominibodies taught in (1) are produced in E.coli. However, nevertheless, at present it cannot be ruled out that the minibodies described in (1) also can be produced in a mammalian host cell as it is required in claim 1. Therefore, (1) is deemed novelty destroying for the above-mentioned claims. Correspondingly, the subject-matter of these claims does not meet the requirements of Art. 33(2)(3) PCT.

In addition, taking into account that the principle underlying the present application, i.e. the provision of a multifunctional compound comprising at least two polypeptides with different receptor or ligand functions which are linked via an immunoglobulin heavy chain CH1 domain and a constant CL domain is already taught in (1) the subject-matters of the remaining claims 3, 4, 8-18, 20-25, 27, 30-32 merely can be considered as obvious alternatives to a person skilled in the art which arise out of the teaching of (1) in combination with the general knowledge of a person skilled in the art. Correspondingly, these claims lack inventive activity and thus do not meet the requirements of Art. 33(3) PCT.

SECTION VIII----------

1). There seems to be a discrepancy in present application since on the one hand at least two of the polypeptides having different receptor or ligand functions lack an intrinsic affinity for one another so that according to the description of present application the presence of VH and VL chains and of scFv fragments in these polypeptides should be excluded by said proviso but on the other hand according to claims 6 and 8 and the examples such domains clearly can be present in said

polypeptides. Relating to this it is also pointed out that according to present claim 1 the minimum number of peptides having different receptor or ligand functions is two!

2). The scope of claim 33 is unclear since due to the alternative "and/or" given in said claim it is unclear whether the claimed composition contains either the multifunctional compound or the polynucleotide or the vector and optionally a proteinaceous compound or whether the claimed composition contains the multifunctional compound, the polynucleotide and the vector optionally in combination with a proteinaceous compound?!

CLAIMS

1. A multifunctional compound, produceable in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains, wherein one of said polypeptide chains comprises, as the only constant region domain of an immunoglobulin heavy chain the CH1-domain and the other polypeptide chain comprises the constant CL-domain of an immunoglobulin light chain, wherein said polypeptide chains further comprise, fused to said constant region domains at least two (poly)peptides having different receptor or ligand functions, wherein further at least two of said different (poly)peptides lack an intrinsic affinity for one another and wherein said polypeptide chains are linked via said constant domains.

2. The multifunctional compound of claim 1, wherein the functional domains, having receptor or ligand function, are C-and/or N-terminally linked to one or both of said constant immunoglobulin domains.

3. The multifunctional compound of claim 1 or 2, comprising at least three functional domains, having receptor or ligand function.

4. The multifunctional compound of anyone of claims 1 to 3, comprising four functional domains, having receptor or ligand function.

5. The multifunctional compound of anyone of claims 1 to 4, wherein at least two domains, having receptor or ligand function, are N-terminally linked to said constant C_H1 or C_L domains.

6. The multifunctional compound of any one of claims I to 5, wherein at least one of said domains, having receptor or ligand function, is in the format of a scFv-fragment or a functional part thereof.

7. The multifunctional compound of any one of claims 1 to 6, wherein at least one of said domains, having receptor- or ligand function, is a T-cell co-stimulatory ligand, an antigen binding region specific for a tumor associated antigen, or a proteinaceous compound providing the primary activation signal for T-cells.

8. The multifunctional compound of any one of claims 6 or 7, wherein said scFv fragment or said functional part thereof comprise the V_H and the V_L regions of the murine anti-human 17-1A antibody M79, the V_H and the V_L regions of the anti-Lewis Y antibody, as shown in Fig. 6, the V_H and the V_L regions of the anti-CD3 antibody TR66, and/or the V_H and the V_L regions of the human anti-human EpCAM antibody as shown in Figure 55.

9. The multifunctional compound of claim 7, wherein the T-cell co-stimulatory ligand is a cell surface molecule or a fragment thereof expressed on antigen-presenting cells (APC).

10. The multifunctional compound of claim 9, wherein the antigen-presenting cell is a dendritic cell.

11. The multifunctional compound of claim 9, wherein the cell surface molecule is selected from the group consisting of B7-1, B7-2, ICAM-1, ICAM-2, ICAM-3, LFA-3 and CD137-ligand.

12. The multifunctional compound of any one of claims 1 to 5, wherein at least one of said domains, having receptor or ligand function, is an immuno-modulating effector molecule or a fragment thereof.

13. The multifunctional compound of claim 12, wherein said immuno-modulating effector molecule or said fragment thereof is selected from the group consisting of cytokines, chemokines, macrophage migration factor (MIF), T-cell receptors and soluble MHC molecules.

14. The multifunctional compound of claim 13, wherein said cytokine is selected from the group consisting of interleukins, interferons, GM-CSF, G-CSF, M-CSF, TNFs and VEGF.

15. The multifunctional compound of claim 13, wherein said chemokine is selected from the group consisting of IL-8, Eotaxin, GROα, GROβ, GROγ, IP-10, MCP-1, MCP-2, MCP-3, MCP-4, MIG, MIP-1α, MIP-1β, NAP-2, RANTES, I309, Lymphotactin and SDS-1.

16. The multifunctional compound of anyone of claims 1 to 5, wherein at least one of said domains, having receptor or ligand function, is FAS ligand (CD 95 L) or a fragment thereof.

17. The multifunctional compound of anyone of claims 1 to 5, wherein at least one of said domains, having receptor or ligand function, is a growth factor or a fragment thereof.

18. The multifunctional compound of anyone of claims 1 to 5, wherein at least one of said domains having receptor or ligand function is an angiogenesis inhibitor or a fragment thereof.

20. The multifunctional compound of any one of claims 1 to 18, wherein said constant domain of an immunoglobulin light chain is of the κ type.

20. The multifunctional compound of any one of claims 1 to 19, wherein said constant immunoglobulin domains and said functional receptor-ligand domains are connected by a polypeptide linker.

21. The multifunctional compound of claim 20, wherein said polypeptide linker comprises an Ig-hinge region or a plurality of glycine, alanine and/or serine.

22. The multifunctional compound of claim 21, wherein said Ig-hinge region is an IgG hinge region.

23. The multifunctional compound of claim 22, wherein the IgG hinge region is the upper hinge region of human IgG_3.

24. The multifunctional compound of any one of claims 1 to 23, wherein said functional domains, having receptor or ligand function, comprise GM-CSF, IL-2 and/or (an) scFv fragment(s) comprising the V_H and the V_L regions of the human-anti-human EpCAM antibody, as shown in Figure 55.

25. The multifunctional compound of claim 24, wherein said GM-CSF and said IL-2 are C-terminally linked to said constant C_H1 or C_L domains and wherein said scFv fragment(s) comprising the V_H and the V_L regions of the human anti-human EpCAM antibody is (are) N-terminally linked to said constant C_H1 or C_L domains.

26. The multifunctional compound of any one of claims 1 to 25, wherein said C_H1 domain is limited to a histidine tag, GST, Staphylococcus protein A, Lex A, a FLAG-tag or a MYC-tag.

27. The multifunctional compound of any one of claims 1 to 26, wherein said functional domains, having receptor or ligand function is or is derived form a non-immunoglobulin domain.

28. A polynucleotide encoding one and/or two polypeptide chains of the multifunctional compound as defined in any one of claims 1 to 27.

29. A vector comprising at least one polynucleotide of claim 28.

30. A mammalian host cell comprising at least one vector of claim 29.

31. The mammalian host cell of claim 30 which is a CHO cell or a myeloma cell.

32. A method of producing the multifunctional compound of any one of claims 1 to 27 comprising culturing the host cell of claim 30 or 31 under conditions that

allow the synthesis and secretion of said multifunctional compound, and recovering said multifunctional compound from the culture.

33. A composition comprising the multifunctional compound of any one of claims 1 to 27, the polynucleotide of claim 28, and/or the vector of claim 29 and, optionally, a proteinaceous compound capable of providing the primary activation signal for T-cells.

34. The composition of claim 33 which is a pharmaceutical composition further comprising, optionally, a pharmaceutically acceptable carrier and/or the diluent and/or excipient.

35. The composition of claim 33 which is a diagnostic composition further comprising, optionally, suitable means for detection.

36. Use of the multifunctional compound of any one of claims 1 to 27, the polynucleotide of claim 28 and/or the vector of claim 29 for the preparation of a pharmaceutical composition for preventing and/or treating malignant cell growth.

37. The use of claim 36, wherein the malignant cell growth is related to malignancies of hemapoietic cells or to solid tumors.

38. The use of claim 37, wherein said malignancies of hernatopoietic cells are lymphomas or leukemias.

39. The use of claim 37, wherein said solid tumors are carcinomas, melanomas or sarcomas.

40. A kit comprising the multifunctional compound of any one of claims 1 to 27 and, optionally, a proteinaceous compound capable of providing the primary activation signal for T-cells.

41. The composition of claim 33, the pharmaceutical composition of claim 34, the diagnostic composition of claim 35 or the kit of claim 40, wherein the proteinaceous compound capable of providing the primary activating signal for T-cells is a bispecific antibody interacting with the T-cell antigen CD3.

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
C 2130 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 05416	28/07/1999	28/07/1998
Applicant		
MICROMET GESELLSCHAFT FÜR BIOMEDIZINISCHE FORSCHUN		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 52

[ ] None of the figures.

[ ] as suggested by the applicant.

[X] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
/EP 99/05416

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K19/00 C12N15/62 C12N15/85 C12N5/10 A61K38/17
G01N33/53 A61K31/70 //C07K16/28,C07K16/30,C07K14/705,
C07K14/535,C07K14/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MÜLLER ET AL.: "The first constant domain (CH1 and CL) of an antibody used as heterodimerization domain for bispecific miniantibodies." FEBS LETTERS, vol. 422, no. 2, 30 January 1998 (1998-01-30), pages 259-264, XP002135067 Amsterdam, The Netherlands abstract figure 1 ---	1,2,5-7, 19,26, 28,29, 33-41
X	WO 97 01580 A (THE SCRIPPS RESEARCH INSTITUTE) 16 January 1997 (1997-01-16) claims --- -/--	1-8, 28-35

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2000	25/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nooij, F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	M. RHEINNECKER ET AL.: "Multivalent antibody fragments with high functional affinity for a tumor-associated carbohydrate antigen." THE JOURNAL OF IMMUNOLOGY, vol. 157, no. 7, 1 October 1996 (1996-10-01), pages 2989-2997, XP002135068 Baltimore, MD, USA abstract figures 2B,8 ---	1-41
A	F. DUCANCEL ET AL.: "Recombinant colorimetric antibodies: construction and characterization of a bifunctional F(ab)2/alkaline phosphatase conjugate produced in Escherichia coli." BIO/TECHNOLOGY, vol. 11, no. 5, May 1993 (1993-05), pages 601-605, XP002135069 USA abstract figure 1 ---	1-41
A	I. KURUCZ ET AL.: "Retargeting of CTL by an efficiently refolded bispecific single-chain Fv dimer produced in bacteria." THE JOURNAL OF IMMUNOLOGY, vol. 154, no. 9, 1 May 1995 (1995-05-01), pages 4576-4582, XP002135070 Baltimore, MD, USA abstract figure 1 ---	1-41
A	A. TRAUNECKER ET AL.: "Bispecific single chain molecules (Janusins) target cytotoxic lymphocytes on HIV infected cells." THE EMBO JOURNAL, vol. 10, no. 12, December 1991 (1991-12), pages 3655-3659, XP000232579 Oxford, GB abstract figure 1 --- -/--	1-41

1

INTERNATIONAL SEARCH REPORT

International Application No
/EP 99/05416

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	P. KUFER ET AL.: "Construction and biological activity of a recombinant bispecific single-chain antibody designed for therapy of minimal residual colorectal cancer." CANCER IMMUNOLOGY, IMMUNOTHERAPY, vol. 45, no. 3-4, November 1997 (1997-11), pages 193-197, XP002076121 Heidelberg, Germany abstract figure 1	1-41
A	B. GERSTMAYER ET AL.: "Costimulation of T cell proliferation by a chimeric B7-2 antibody fusion protein specifically targeted to cells expressing the erbB2 proto-oncogene." THE JOURNAL OF IMMUNOLOGY, vol. 158, no. 10, 15 May 1997 (1997-05-15), pages 4584-4590, XP002116142 Baltimore, MD, USA abstract figure 1A	1-41
A	EP 0 404 097 A (BEHRINGWERKE AG) 27 December 1990 (1990-12-27) the whole document	1-41
A	EP 0 517 024 A (BEHRINGWERKE AG) 9 December 1992 (1992-12-09) the whole document	1-41
A	WO 95 09917 A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 13 April 1995 (1995-04-13) figure 3	1-41

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/05416

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9701580	A	16-01-1997	AU	6340996 A	30-01-1997
EP 404097	A	27-12-1990	DE	3920358 A	17-01-1991
			AT	142230 T	15-09-1996
			AU	639241 B	22-07-1993
			AU	5762190 A	03-01-1991
			CA	2019559 A	22-12-1990
			DE	59010480 D	10-10-1996
			DK	404097 T	10-02-1997
			ES	2093623 T	01-01-1997
			GR	3021109 T	31-12-1996
			IE	76715 B	22-10-1997
			JP	2978210 B	15-11-1999
			JP	3048699 A	01-03-1991
			KR	183980 B	01-04-1999
			PT	94443 A,B	08-02-1991
			RU	2096459 C	20-11-1997
			US	5591828 A	07-01-1997
EP 517024	A	09-12-1992	DE	4118120 A	10-12-1992
			AT	156858 T	15-08-1997
			AU	664992 B	14-12-1995
			AU	1735692 A	10-12-1992
			CA	2070233 A	04-12-1992
			DE	59208789 D	18-09-1997
			DK	517024 T	23-03-1998
			ES	2106796 T	16-11-1997
			GR	3024931 T	30-01-1998
			JP	6128297 A	10-05-1994
			US	5959083 A	28-09-1999
WO 9509917	A	13-04-1995	NONE		